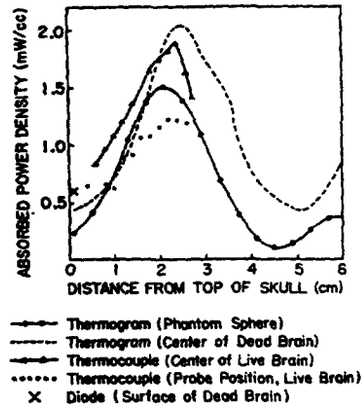

Fig. 22. Measured absorbed power patterns in cat brain due to microwave radiation from 918-MHz aperture source (spacing 8 cm with 1-W input power).

applied to the head have more of an effect on the later latency. The changes are reversible and have time constants that seem to be directly associated with the thermal effect of microwaves, provided the temperature does not exceed 42°. The threshold for both temperature changes and latency changes was found to correspond to a maximum power absorption level between 2.5 and 5.0 mW/cm² at the center of the brain. Table III indicates that this corresponds to an indicated power density of 3.0 to 6.0 mW/cm² as measured in the unoccupied stereotaxic support by the Narda monitor. It would take a plane wave power density of 5 to 11 mW/cm², however, to produce the same maximum power absorption in the human brain, assuming it can be represented by the simple model illustrated in Fig. 4. On the other hand, Fig. 5 indicates it would take an incident power density of only 0.5 to 1.0 mW/cm² at a frequency of 2450 MHz to produce the same maximum power absorption in the animal head represented by a 3-cm-diameter sphere.

E. Medical Applications

The medical applications of microwaves can be classified into two areas—heating of tissues and diagnostic. The former includes the most historic application, diathermy or therapeutic heating of tissues, and newer applications, including rewarming of refrigerated whole blood, thawing of frozen human organs, production of differential hyperthermia (elevated body temperature) in connection with cancer treatment, and rapidly reversing a patient's hypothermic state (low body temperature) in connection with open heart surgery. Diagnostic applications include dielectric constant measurements to assess the properties and condition of certain biological tissues and reflectance and transmission measurements to assess significant parameters such as blood or respiratory volume changes.

1) Diathermy: The oldest application of microwaves to medicine is "diathermy," a clinical technique used to achieve "deep heating," i.e., heat induced in tissue beneath the skin and subcutaneous fatty layers. Sufficient deep heating can elevate the temperature to the point where therapeutic benefits are achieved through local increases in metabolic activity and in blood flow by dilation of the blood vessels. The beneficial results are believed to arise from the stimulation of healing and defense reactions of the human body. Diathermy has been used successfully in the treatment of musculoskeletal diseases, such as arthritic and rheumatic conditions, fibrositis, myositis, pain, sprains and strains, and many other ailments too numerous to mention here. A complete treatment of the subject is covered in a work by Licht [78]. The deep heating cannot be obtained with heating pads or infrared rays, but must be accomplished by the transformation of certain forms of physical energy, such as ultrasound, radio, or microwave, into heat beneath the subcutaneous fat layer. Both microwave energy and ultrasound produce the required heating in the deeper tissues, though lately ultrasound appears as the most popular method due to its deeper penetration. Part of this stems from the historic poor choice of a microwave diathermy frequency of 2450 MHz discussed previously. Clearly, the presently used frequency does not provide a good method for achieving deep heating with minimal surface heating. This problem has been discussed in great detail by Schwan [45], [46]. There is considerable room for improvement of diathermy through the application of more sophisticated microwave and clinical techniques.

2) Differential Hypothermia in Cancer Treatment: Research on a new application of microwave heating of body tissues in the treatment of cancer is now being conducted [4]. The technique involves the use of microwaves to selectively and uniformly heat the cancer or tumor area while the remainder of the body is maintained in a hypothermic condition 25°C below normal body temperature. A very toxic anticancer drug is then administered to the subject. The cooler tissues will absorb very little of the drug while the warmed tumor will have a metabolic rate that allows a significant amount of the drug to be absorbed. Through the combined use of selected frequencies, dielectric-loaded waveguide apertures, and surface cooling, controlled heating patterns can be applied to the cancer area. Recent experiments on mice indicate that 75 percent of the tumors disappear after 4 to 5 h of treatment.

3) Warming of Human Blood: The warming of refrigerated bank blood from its 4° to 6°C storage temperature to body temperature prior to transfusion is important to prevent dangerous cardiac and general body hypothermia. This has been done in the past by passing the blood through a long small-core plastic tubing that is coiled in a thermostatically controlled water bath. The heat exchanger offers considerable resistance to the blood, slowing down the rate of transfusion which presents problems when rapid blood replacement is necessary. Restall *et al.* [3] has developed a microwave blood warmer that will heat a unit of blood (approximately 500 ml) in its original plastic container from 4°–6°C to 35°C in 1 min. This warmed blood can then be rapidly administered to the patient since both the viscosity has been lowered and the warming coil eliminated. The unit is warmed by rotating it in a microwave cavity driven by a 2450-MHz 1000-W magnetron. Extensive laboratory tests indicate no deleterious effects in the blood. Transfusions to 37 volunteer patients also indicate no abnormal effects.

4) Rapid Elimination of Hypothermia: A standard technique used in open heart surgery is to reduce the body temperature in order to induce a hypothermic state prior to surgery. Hypothermia slows down the metabolic rate of the body cells so that nutrients and oxygen requirements are reduced sufficiently to allow the heart to be stopped for surgery. Surface *cooling* is desired prior to surgery since the peripheral body cells are cooled *before* the body core temperature is reduced to the point where the blood cannot provide nutrients and oxygen. During the rewarming stage after surgery, however, *core heating* is desired so that blood temperature is sufficient to allow proper metabolism prior to the

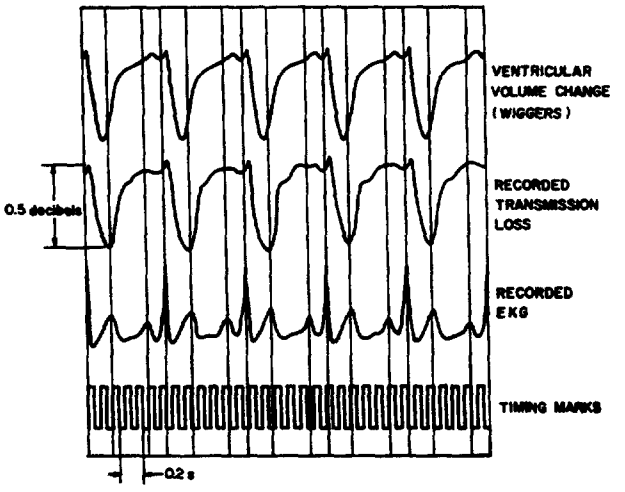

Fig. 23. Comparison of cardiac ventricular volume change with recorded microwave transmission loss through chest cavity.

rewarming of peripheral cells. If surface heating is used, peripheral cells will require oxygen and nutrients at a level that the blood cannot provide due to the lower body core temperature. Core heating can be provided for adults and large children by pumping the blood through heat exchangers. This is a time-consuming process, however, that restricts the total time allocated for surgery. This type of core heating cannot be used for infants below a certain size due to physical limitations of the apparatus. Microwaves do offer a method for rapidly achieving the core heating for any size patient by selectively heating certain portions of the body. Experiments have just begun on the development of such a device by Guy.

5) Rapid Thawing of Frozen Tissues: Rapid thawing of human organs or other biomaterials such as semen which are cryopreserved can be accomplished with microwaves [79], [80]. Many studies have shown that an increase in the survival of biological materials is associated with rapid thawing rates. With proper developmet of microwave applicators, thawing rates up to 10 times faster can be achieved over conventional methods.

6) Diagnostic Studies: Moskalenko [81], [82] has formulated methods for assessing the changes in microwave or shortwave reflectance and transmission which are caused by significant parameters such as blood or respiratory volume changes. Guy has demonstrated the feasibility of Moskalenko's method by measuring the transmission loss of a 915-MHz microwave beam as it passes through the human chest. Fig. 23 illustrates that the variation in microwave loss is proportional to the ventricular volume changes in the heart. The potentialities of this approach appear very favorable. Lonngren [83] has been able to determine the degree of pulmonary emphysema in postmorten analysis of a lung by measuring the dielectric properties of the dried diseased portions. This technique can also be applied to study the composition of many biomaterials whether in small samples or in a living subject. A great deal can be learned about the composition of biomaterials and biological systems through measurements of their electrical properties at microwave frequencies. An example is the strong dependence of the refraction index and absorption characteristics of various tissues on their water content. Thus it is theoretically possible to assess the water content of subcutaneous fat in a living subject without penetrating the skin. Another possibility is the analysis of biological membrane systems with respect to the role of structured or bound water in their function by measuring the refractive index and absorption characteristics [84]. Other applications are the large-scale modeling of certain molecular structures of macro-molecules so that some of the dynamic reactions observed at optical frequencies can be more easily studied at microwave frequencies. The optical activity of certain biological helical molecules prompted several studies involving model systems of copper helices exposed to electromagnetic radiation [85], [86]. Certain aspects of the thermoregulatory system can be studied by using microwaves as a controlled source of heat [87]–[90].

III. Optical Effects

A. Introduction

Optical radiation plays a very significant role in mankind. On the whole, man is very well adapted to the sun's optical and infrared radiation and depends on it for warmth, the processing of food through photosynthesis, and as the principal source of sensory information through the eyes. Optical hazards to man are few, and mostly come from artificial sources such as lasers. The ultraviolet portion of the spectrum can cause superficial cell damage (sunburn).

Despite the important role of optical energy in the animal and plant world, its use in medical and biological applications has been limited. Examples include quantitative biochemical analysis in the clinical chemistry laboratory, optical and electron microscopy, endoscopy (including the use of coherent fiberoptic bundles for probing in the body), spectroscopy, and holography. New principles, techniques, and devices, such as lasers, light-emitting diodes, fiberoptics, optical data processing, holography, integrated optical circuits, phototransistors, etc., are now available which are expanding the use of light in biological applications.

Of particular interest in this paper are the optical propagation characteristics in biological materials. We will not generally be concerned with cell damage and hazardous effects that are confined to the UV spectrum or high intensities. These are described elsewhere [10]. Optical propagation in biological materials is dominated by scattering, because the cellular structure creates medium inhomogeneities of the order of an optical wavelength. There are many optical absorption peaks caused by a variety of biochemical molecules which create a variable optical absorption as a function of wavelength. These combined scattering and absorption properties will be illustrated for some selected biomaterials, and an analytical foundation will be laid for describing these effects.

B. Biological Materials

It is important to know some of the characteristics of cells and tissues in the human body in order to appreciate the optical wave interactive processes that can occur. Very little will be said about anatomical configurations; the interest here is primarily in tissue and cellular structure.

1) Cells: Cells come in all sizes and shapes, and are commonly several microns in diameter. Muscle cells may be a few millimeters long, and nerve cells over a meter long. The gross characteristics of a cell include a thin membrane that holds the cell together, cytoplasm which is a gel-like material within the membrane, and usually a nucleus. Within the cytoplasm are several types of smaller structures called organelles which perform specific metabolic functions. Vesicles partition the cell interior so that materials may be separated and com-

partmentalized for specific chemical reactions. Organelle sizes vary from fractions of a micron up to a micron, and are thus close to optical wavelengths. Cell membranes are approximately 75 Å thick.

2) Tissues: Cells are grouped together and combined with other materials to form several characteristic types of materials called tissues. There are four basic tissues types—epithelial, connective, muscular, and nervous.

Epithelial tissue consists of cells in single or multilayered membranes that cover or line a surface. Epithelial tissues perform the functions of protection and regulation of secretion and absorption of materials. Simple squamous tissue is a single layer of flat cells, commonly used in blood vessels where a very thin lining is necessary to allow rapid diffusion of electrolytes. Cuboidal and columnar tissues are constructed from cells of cube and column shapes, and are found in airways, the digestive tract, and the bladder.

Connective tissue consists of cells and nonliving materials such as fibers and gelatinous substances which support and connect cellular tissue to the skeleton. Connective tissue comprises much of the intercellular substances that perform the important function of transporting materials between cells. Specialized examples of connective tissue are bone and cartilage. Subdermal connective tissue contains collagen and elastic fibers which give the skin its mechanical properties of toughness and elasticity.

Muscle tissue consists of cells that are 1–40 mm in length and up to 40 μ in diameter. Muscles contain an extensive blood supply, and are thus filled with blood vessels and capillaries with their attendant connective tissue. A large group of muscle fibers are commonly bound together in a sheath. Skeletal muscle has a regular internal striated fine structure due to an ordered array of protein filaments of the order of 100 Å in diameter and 1–2 μ long. This structure has been used as an optical diffraction grating to measure the filament lengths, spacings, and motion during muscle contraction.

Nervous tissue is used to sense, control, and govern body activity. It consists of nerve cells called neurons. Neurons have long projections called axons, which are very analogous to transmission lines. Neurons are located in every portion of the body, sending information to the CNS from a variety of information receptors, and from the CNS to muscles, organs, glands, etc.

3) Erythrocytes: The normal shape of the erythrocyte (red blood cell) is a biconcave disk. There are no internal organelles or supporting structures in the mature erythrocyte, thus the biconcave shape is due to a variety of other factors such as molecular and chemical constitution, membrane properties, and osmotic pressures. The erythrocyte broad diameter is about 7 μ and its thickness varies from 1 μ in the center to 2 μ near the edges. The cell consists of hemoglobin molecules packaged in a thin membrane. A principal function of the erythrocyte is to absorb and release oxygen and carbon dioxide at the cell surface, and the biconcave shape is an ideal one for this purpose. The erythrocyte contains no nucleus, and may not divide to form new cells. Erythrocyte formation occurs in the bone marrow. Young erythrocytes are continually being fed into the blood stream and old ones absorbed and reprocessed in the liver. Under normal conditions, there are approximately 5×10^6 erythrocytes per mm^3. About 40 percent of the volume of whole blood consists of erythrocytes; the remaining 60 percent is a nearly transparent solution of water and salt with a variety of electrolytes and protein molecules. The volume percentage of erythrocytes in whole blood is called hematocrit H.

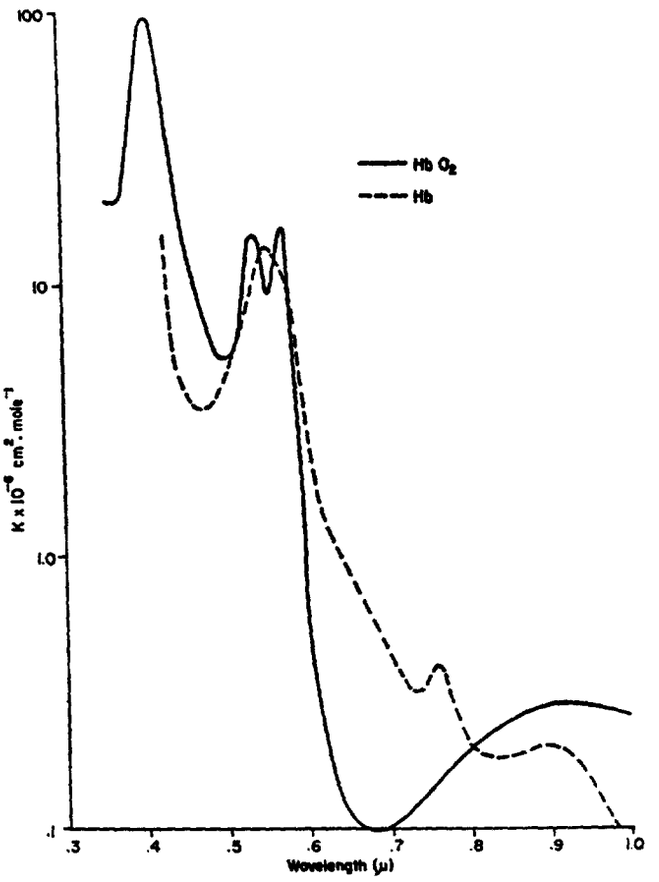

Fig. 24. Optical absorption spectrum of hemoglobin and oxyhemoglobin plotted in terms of specific absorption coefficient κ versus wavelength. The difference between the two curves causes the change in color of blood as its oxygen content changes and makes possible optical spectroscopic techniques for measuring oxygen saturation.

C. Optical Properties of Biological Materials

Very little is known about the optical properties of most biological materials. There is considerable data on hemoglobin solutions and whole blood, some data on skin, and some interest in cellular effects [91]–[95]. Ultraviolet irradiation has been a subject of interest for many years due to the hazards involved [96], [97].

1) Blood: Light has been used for many years to determine the oxygen content in blood. The normal healthy pink appearance of a person compared to a grey color or "blue baby" is a common diagnostic tool based on optical spectroscopic effects in blood. Erythrocytes contain hemoglobin molecules, Hb, which are easily oxygenated to oxyhemoglobin molecules HbO_2. An important parameter is oxygen saturation OS, defined as the ratio of HbO_2 to total hemoglobin. There is an index of refraction discontinuity between the erythrocyte and its surrounding plasma medium (about 1.40 to 1.35) [98], thus scattering occurs which complicates the optical measurement of hemoglobin contained inside the erythrocyte. Thus in order to obtain the absorption spectrum of the hemoglobin molecules, it is useful to rupture the erythrocyte membrane and release the hemoglobin into solution. When this is done, the medium is called hemolyzed blood. The specific absorption coefficients (defined later) of Hb and HbO_2 is hemolyzed blood are illustrated in Fig. 24, obtained from composite data by

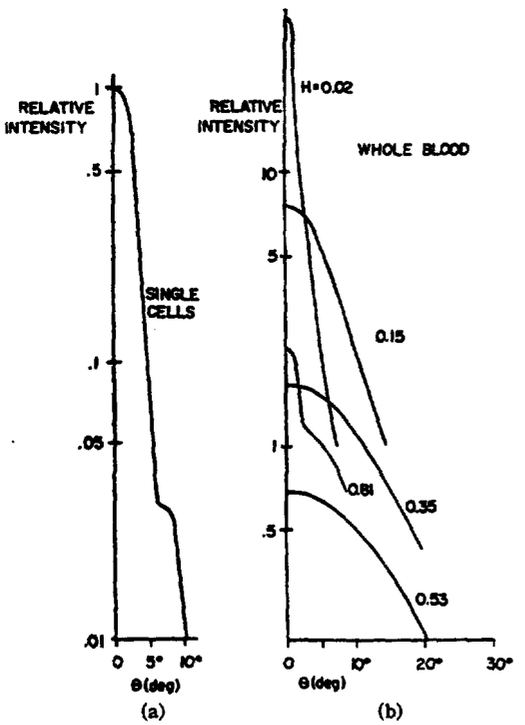

Fig. 25. Forward scattered intensity plotted versus scattering angle θ for erythrocytes. (a) Isolated erythrocytes. (b) Whole blood, sample thickness $d=75\ \mu$, $\lambda=0.8\ \mu$, for different hematocrit values.

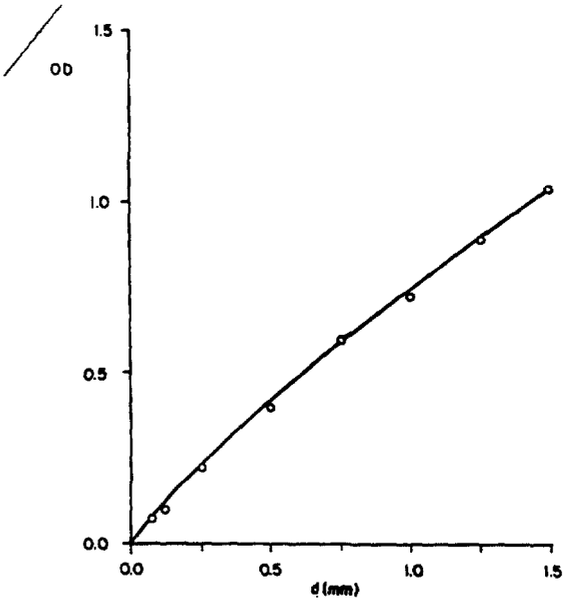

Fig. 26. Optical density plotted versus blood layer thickness d. Experimental data points are shown for $\lambda=0.80\ \mu$, $H=0.35$.

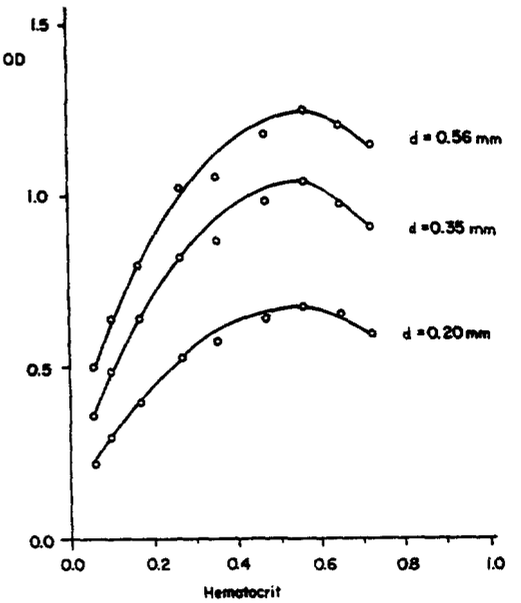

Fig. 27. Optical density plotted versus hematocrit for different blood sample thicknesses d, for $\lambda=0.80\ \mu$.

Barer [99] and Horecker [101]. A strong absorption band is centered at 414.5 nm, called the Soret band, with minor absorption peaks in the 550-nm region. Oxyhemoglobin HbO_2 has low absorption in the red portion of the spectrum compared to Hb. Thus blood "looks" red when oxyhemoglobin molecules are predominant. At $\lambda=548$, 568, 587, and 805 nm, the absorption values are equal, and these wavelengths are called *isosbestic* points.

Observers have noted that there is a greater net absorption when hemoglobin is packaged in erythrocytes (whole blood) as compared to being in solution (hemolyzed blood). The increased absorption is due to erythrocyte scattering effects. The relative intensity of forward-scattered light of isolated erythrocytes as a function of scattering angle θ has been obtained experimentally [101]–[103] and is shown in Fig. 25(a). The shoulder in the curve near 8° has been attributed to a secondary diffraction peak effect. Scattering data for whole blood have also been obtained [104], as shown in Fig. 25(b). Note that for low hematocrit H a very narrow beam of transmitted light is obtained, indicating that much of the transmitted light is not scattered. As hematocrit increases, the transmitted beam broadens, indicative of increased scattering. The $\theta=0°$ intensity is lowered with increased H due to increased absorption and scattering. Note the striking effect at high hematocrit $H=0.81$ of increased transmittance and the reappearance of an unscattered narrow beam on top of a broader scattered beam. The increased transmittance is due to a decreased amount of scattering, as the absorption must necessarily increase. Scattering for low hematocrit values principally occurs at the erythrocyte sites. Increased hematocrit means an increased number of erythrocytes and increased scattering. For higher hematocrit values $H>0.5$, the erythrocytes pack together to form a homogenous mass of absorbing hemoglobin material, and the scattering occurs at the plasma cavities located between masses of red blood cells. The plasma cavities decrease with increased hematocrit, thus decreased scattering is observed with increased hematocrit at larger H values.

Measurements have been obtained for transmittance T and reflectance R of thin whole blood samples. Fig. 26 shows density $OD=\log_{10}(T^{-1})$ versus sample thickness d at $\lambda=0.80\ \mu$. Note that a straight line Lambert–Beer law result is not obtained. The curvature is due to scattering effects, as described later. Fig. 27 shows an increase and subsequent decrease in OD versus H, for different d values [104]. Similar results for reflectance are shown in Fig. 28 for different sample depths [105]. The increase and subsequent decrease in OD and reflectance as a function of hematocrit is caused by changes in scattering from the erythrocytes.

2) Skin: Optical (particularly ultraviolet) effects in skin

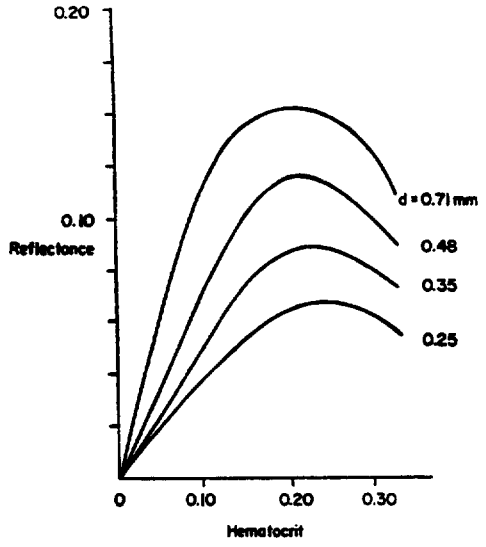

Fig. 28. Optical reflectance plotted versus hematocrit for different blood sample thicknesses d, for fully oxygenated blood at $\lambda = 0.63\ \mu$.

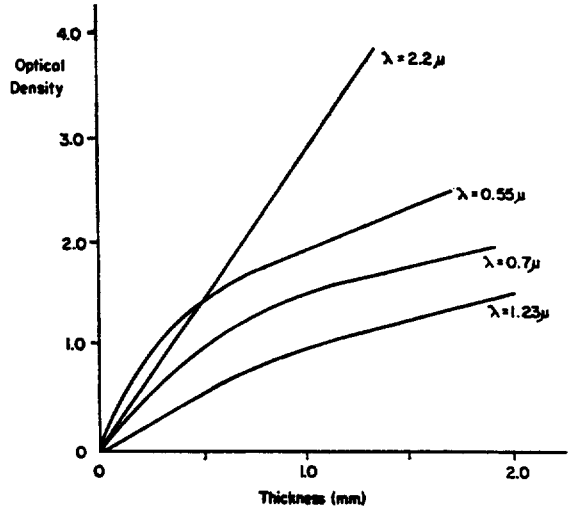

Fig. 29. Optical density plotted versus skin layer thickness of white human skin at four wavelengths.

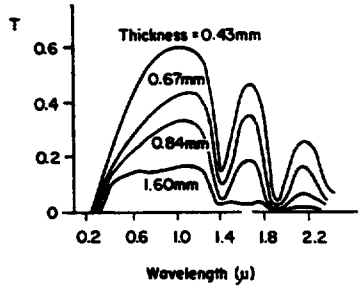

Fig. 30. Spectral transmittance of excised white human skin in the visible and infrared spectrum.

have been studied extensively [106]. A comprehensive paper by Hardy *et al.* [107] establishes the scattering and absorbing properties of skin. Fig. 29 shows *OD* versus skin layer thickness for several wavelengths [107]. The 2.2-μ curve is a straight line indicating that at this longer wavelength, skin transmission is largely governed by the Lambert–Beer law. At shorter wavelengths, considerable bending of the curves is

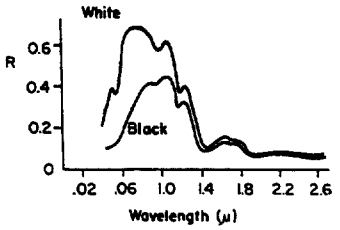

Fig. 31. Reflectance spectrum of very fair complexioned white skin, and very dark American black skin in the visible and near infrared.

observed, indicating the presence of other phenomena such as scattering. The transmittance versus wavelength characteristics for skin in the ultraviolet-to-infrared regions are illustrated in Fig. 30. Note that transmission rises very rapidly as wavelength is increased above 0.3 μ. The skin heavily absorbs UV radiation, providing a protection for the underlying tissues that are damaged by UV. The inefficiency in this protection gives rise to sunburn. Beyond 1.4 μ, the transmission curves follow closely the transmission characteristics of water.

Reflectance versus wavelength from both light and dark skins has been measured [108], [109], and is shown in Fig. 31. Reflectance in the near infrared is determined by scattering sites in skin and the transmission characteristics of water.

D. Scattering and Absorption

A homogeneous absorbing medium with no scattering obeys the simple one-dimensional exponential law of absorption called the Lambert–Beer law. The absorption per centimeter α causes a reduction in wave intensity I^+ traveling in the $+z$ direction according to $dI^+ = -\alpha I^+ dz$. This is integrated to obtain the Lambert–Beer law

$$I^+(z) = I^+(0)e^{-\alpha z} \tag{11}$$

where $I^+(0)$ is the intensity at $z = 0$. Transmittance T becomes $T = e^{-\alpha z}$. The Lambert–Beer law is often applied to a solution of molecules that absorb optical energy, for example, various protein molecules. Clearly, α is dependent on the molecular concentration C as well as the specific absorption properties of the molecular species given by the parameter κ:

$$\alpha = C\kappa.$$

The concentration C is expressed in moles·cm^{-3}, and κ, defined as the *specific absorption coefficient* for the material, has the dimensions cm^2·mole^{-1}. Values of κ for Hb and HbO_2 were given previously in Fig. 24. For a sample thickness d, optical density becomes

$$OD = 0.4343C\kappa d. \tag{12}$$

Note that for a purely absorbing material described by the Lambert–Beer law, a plot of *OD* versus d results in a straight line, the slope of which is proportional to the specific absorption coefficient for the absorbing medium and the concentration. *OD* measurements can be used to determine the concentration of molecular species, knowing κ and d.

When the radiation wavelength approaches the size of an object or inhomogeneity in the medium, scattering occurs. substantial deviations from the Lambert–Beer law due to scattering are present in whole blood, and in skin for the shorter wavelengths. The historical analytical approach to this problem originated with the work of Schuster [110] in

his attempt to describe optical scattering through atmospheres of distant stars. This work was subsequently modified [111]–[113], and popularized by Kubelka and Munk [114], and later by Kubelka [115]. Subsequent modifications have been extensive [116]–[119]. We are particularly interested in the application of Schuster's work to the understanding of optical absorption and scattering in biological material, such as blood and skin [120]–[122].

Schuster's two-flux theory is one-dimensional and applies only to diffuse flux. A $+z$ traveling diffuse intensity I^+ generates a $-z$ propagating diffuse intensity I^- due to scattering sites in the absorbing material. The scatterers in the material are characterized by an absorption cross section σ_a and a backscattering cross section σ_s^-. The differential intensity dI^- generated within dz for a scatterer volume density ρ is $dI^- = \rho\sigma_s^- I^+ dz$. By analogy, the amount of I^+ generated by the presence of I^- is $dI^+ = \rho\sigma_s^- I^- dz$. General differential relations describing I^+ and I^- in the material may now be written. Each wave loses intensity due to absorption and backscattering, and gains intensity from backscattering of the other wave.

$$\frac{dI^+}{dz} = -\rho(\sigma_a + \sigma_s^-)I^+ + \rho\sigma_s^- I^- \tag{13}$$

$$\frac{dI^-}{dz} = \rho(\sigma_a + \sigma_s^-)I^- - \rho\sigma_s^- I^+. \tag{14}$$

Note that when $\sigma_s^- = 0$ in (13), then (11) is obtained with $\alpha = \rho\sigma_a$. Since ρ is proportional to C, the specific absorption coefficient κ is proportional to σ_a.

We desire solutions to (13) and (14) for a semi-infinite absorbing and scattering medium occupying the space $z > 0$. It is assumed that at $z = 0$, an I^+ wave is impressed on the medium of intensity $I^+(0)$.

Exponential solutions are appropriate.

$$I^+(z) = I^+(0)e^{-\rho\sigma z} \tag{15}$$

$$I^-(z) = I^-(0)e^{-\rho\sigma z} \tag{16}$$

where $I^-(0)$ and σ are

$$I^-(0) = \frac{\sigma_a + \sigma_s^- - \sigma}{\sigma_s^-} I^+(0) \tag{17}$$

$$\sigma = \sigma_a \sqrt{1 + 2\frac{\sigma_s^-}{\sigma_a}}. \tag{18}$$

Of great interest in practical biomedical instrumentation is reflectance R, defined as $I^-(0)/I^+(0)$:

$$R = 1 + \frac{\sigma_a}{\sigma_s^-}\left(1 - \sqrt{1 + 2\frac{\sigma_s^-}{\sigma_a}}\right). \tag{19}$$

Solutions of (13) and (14) for a slab medium occupying the space $0 < z < d$ are now sought. In this case, an exponential solution of the form

$$I^+(z) = C_1 e^{\rho\sigma z} + C_2 e^{-\rho\sigma z} \tag{20}$$

is obtained, and from (13) and (14) the corresponding solution for I^- is

$$I^-(z) = \frac{\sigma_a + \sigma_s^- + \sigma}{\sigma_s^-} C_1 e^{\rho\sigma z} + \frac{\sigma_a + \sigma_s^- - \sigma}{\sigma_s^-} C_2 e^{-\rho\sigma z}. \tag{21}$$

It is again assumed that $I^+ = I^+(0)$ at $z = 0$. At $z = d$ we set $I^-(d) = 0$. Equations (20) and (21) may be solved in accordance with these boundary conditions to obtain the results

$$\frac{I^+(z)}{I^+(0)} = \frac{e^{\rho\sigma z} - Ae^{\rho\sigma(2d-z)}}{1 - Ae^{2\rho\sigma d}} \tag{22}$$

$$\frac{I^-(z)}{I^+(0)} = \frac{\sigma_a + \sigma_s^- + \sigma}{\sigma_s^-}\left(\frac{e^{\rho\sigma z} - Ae^{\rho\sigma(2d-z)}}{1 - Ae^{2\rho\sigma d}}\right) \tag{23}$$

where σ is given (18), and

$$A = \frac{\sigma_a + \sigma_s^- + \sigma}{\sigma_a + \sigma_s^- - \sigma}. \tag{24}$$

Using (22) and (23), expressions for reflectance and transmittance for a slab medium may be obtained.

$$R = \frac{\sigma_a + \sigma_s + \sigma}{\sigma_s^-}\left(\frac{1 - e^{2\rho\sigma d}}{1 - Ae^{2\rho\sigma d}}\right) \tag{25}$$

$$T = \left(\frac{1 - A}{1 - Ae^{2\rho\sigma d}}\right)e^{\rho\sigma d}. \tag{26}$$

For application of these relations to whole blood, one must write the dependence of scattering on hematocrit H. The absorption cross section σ_a depends on the relative proportion of hemoglobin and oxyhemoglobin in the erythrocyte, and is believed not to vary significantly with H. The backscattering parameter σ_s^- clearly depends on H. An isolated erythrocyte has a backscattering cross section denoted as $\hat{\sigma}_s^-$. As hematocrit increases, the scattering due to erythrocytes decreases significantly, as explained previously. Hematocrit is related to scatterer density ρ and erythrocyte volume v by the relation $H = \rho v$. The scatterer parameters become

$$\rho\sigma_a = \frac{H\sigma_a}{v} \tag{27}$$

$$\rho\sigma_s^- = \frac{\hat{\sigma}_s^- H(1 - H)}{v} \tag{28}$$

where the simple multiplying factor $(1-H)$ describes the variation of σ_s^- from $\hat{\sigma}_s^-$ at $H = 0$ to zero at $H = 1$ [123].

Although the two-flux theory has been very popular and has helped to explain qualitatively some optical effects in biological materials, quantitative results have not been obtained since the theory is restricted to a one-dimensional geometry and to diffuse flux. These restrictions greatly limit the applicability to experimental apparatus. Nonetheless, application of (25) and (26) describes very well the qualitative behavior of Figs. 26–28. In addition, the equations describe observed changes in OD and R with oxygen saturation which affects σ_a. We can conclude that the parabolic-shaped OD and R versus H curves in Figs. 27 and 28, as well as the nonlinear OD versus d curves in Figs. 26 and 29, are due to scattering effects in the absorbing material.

E. Optical Diffusion Theory

More sophisticated attempts to describe wave scattering and absorption effects can be categorized into either a "phenomenological" approach based on Schuster's work and progressing into neutron transport theory and radiative transport theory [124], [125], or an "analytic" approach based on Maxwell's field equations and dealing with averaged fiel

quantities [126]. An optical diffusion theory that assumes isotropic scattering has emerged from the phenomenological approach as a means of describing some of the observed phenomena in biological materials with a promising degree of quantitive precision and with analytical simplicity [122], [127], [128]. A simple visual observation of light propagation in blood is highly suggestive of a diffusion process, despite the fact that erythrocyte scattering is known to be not isotropic (see Fig. 25). Quantitative measurements have since shown the partial validity of a photon diffusion theory for blood [129]–[131].

The basic integral equation from radiative transfer theory and other approaches is [132]

$$\rho(r) = \rho_0(r) + \int_{V'} \frac{\omega\rho(r')e^{-R/\lambda}}{4\pi\lambda R^2}\, dV' \tag{29}$$

where

r	field point position (x, y, z),
r' and V'	source point position (x', y', z') or source volume in the integral.
ρ	total photon density,
ρ_0	density of unscattered photons (from an optical source),
ω	probability that a photon collision results in scattering (not absorption),
λ	photon mean free path,
R	$=\lvert r-r'\rvert$.

This integral equation may be obtained from photon conservation considerations taking into account absorption and isotropic scattering [133]. It is assumed that the probability for a photon to have a free flight over a distance R is $\exp(-R/\lambda)$.

The $\exp(-R/\lambda)$ term in the integral of (29) causes the integrand to receive its major contributions close to $R=0$, where $\lvert r'\rvert \approx \lvert r\rvert$. This suggests an approximation for $\rho(r')$ in the integrand consisting of the first term in a Taylor's series expansion.

$$\begin{aligned}\rho(r') &\cong \rho(r) + [(r' - r)\cdot\nabla]\rho(r)\\ &= \rho(r) - R\cdot\nabla\rho(r).\end{aligned}$$

Using this approximation in (29) gives the standard diffusion differential equation

$$\left(\nabla^2 - \frac{3(1-\omega)}{\omega\lambda^2}\right)\rho = -\frac{3\rho_0}{\omega\lambda^2} \tag{30}$$

which describes the spatial distribution of total photon density ρ in terms of the unscattered source photon density ρ_0. The optical intensity or photon flux, denoted as Γ_s, is desired. Γ_s is related to ρ by the expression $\Gamma_s = -D\nabla\rho$, where D is the diffusion coefficient. In terms of the parameters used here, $D=\omega v\lambda/3$, where v is the photon velocity.

By the nature of diffusion theory, the basic differential relation (30) does not apply near a boundary. A simple approximate boundary condition commonly used is $\rho=0$. More rigorously, one must use the integral form (29) in order to obtain a relation between the parameters that hold at the boundary. The planar boundary between a diffusing medium and a nondiffusing medium requires an evaluation of the integral over a half-space, assuming $\rho(r')=0$ in the other half-space. This results in a relation between ρ, $\nabla\rho$, and ρ_0 at the boundary [133]:

$$\rho(1 - \omega/2) + \frac{\omega\lambda}{4}\nabla\rho\cdot\hat{n} = \rho_0 \tag{31}$$

where $\hat{n}$ is a unit vector pointing normally away from the diffusing medium. Note that for $\rho_0=0$, $\omega=1$, (31) gives

$$\rho = 0.5\lambda\frac{\partial\rho}{\partial n} \tag{32}$$

whereas the accepted value from radiative transfer theory is

$$\rho_s = -0.71\lambda\frac{\partial\rho_s}{\partial n} \tag{33}$$

where $\rho_s=\rho-\rho_0$. These two boundary relations are for different photon parameters and derived under different approximations, so it is difficult to say which is more correct for this application. The form of the results is identical.

It has been found that use of the differential equation with the boundary condition gives surprisingly good results. In light of the usual difficulty encountered in trying to solve the integral equation, the diffusion theory approximation is extremely important and valuable. The diffusion equation can be used to find ρ, where ρ is required to satisfy a boundary condition. Photon flux Γ_s is then obtained from ρ.

Solutions to diffusion equation (30) can be obtained using Green's function techniques. For example, for an infinite scattering medium, one can use the infinite medium Green's function to write the solution for ρ:

$$\rho(r) = \frac{3}{\omega\lambda^2}\int_{V'}\frac{e^{-R/\lambda_d}}{4\pi R}\rho_0(r')dV' \tag{34}$$

where $\lambda_d=\lambda\sqrt{\omega/3(1-\omega)}$ is a diffusion "penetration depth." Simple solutions are obtained in the far-field region where $\lvert r\rvert \gg \lvert r'\rvert$ at positions far from the region of source photons ρ_0:

$$\rho(r) \cong \frac{3}{4\pi\omega\lambda^2}\frac{e^{-r/\lambda_d}}{r}\int_{V'}\rho_0(r')dV'.$$

For a slab medium in the region $0<z<d$, a Green's function solution has been obtained using the simple $\rho=0$ boundary condition at $z=0$ and d [131]. Assuming no ϕ variations in a cylindrical r, ϕ, z coordinate system gives

$$\begin{aligned}\rho = {} & \frac{6\sin\left(\frac{n\pi z}{d}\right)}{d\omega\lambda^2}\\ & \cdot\sum_{n=1}^{\infty}\int_0^{\infty}\int_0^{d}\left[\sin\left(\frac{n\pi z'}{d}\right)\rho_0(z', r')dz'\right]\\ & \cdot\begin{bmatrix} I_0(\lambda_n r) & K_0(\lambda_n r')\\ I_0(\lambda_n r') & K_0(\lambda_n r)\end{bmatrix} r'dr'\end{aligned} \tag{35}$$

where

$$\lambda_n^2 = \left(\frac{1}{\lambda_d}\right)^2 + \left(\frac{n\pi}{d}\right)^2.$$

The upper terms in the square brackets are used for $\lvert r'\rvert > \lvert r\rvert$, and the lower terms are used for $\lvert r'\rvert < \lvert r\rvert$. This result has been applied to the case of a cylindrical beam of incident

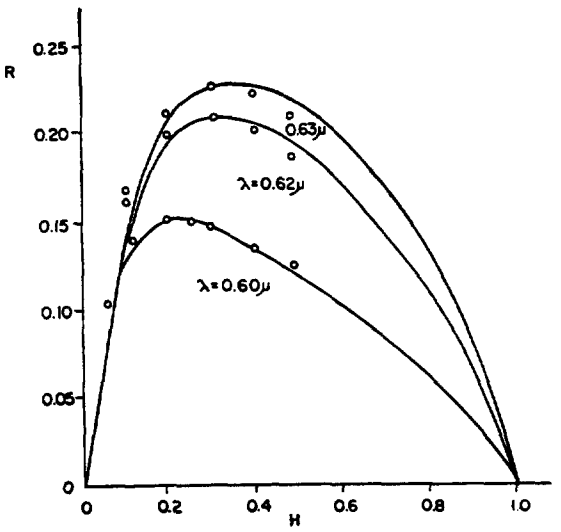

Fig. 32. Reflectance plotted versus hematocrit of whole human blood at three red wavelengths. Experimental data are shown by the circles, and theoretical diffuse reflectance curves from optical diffusion theory are shown by the solid lines, normalized at peak reflectance for the $\lambda = 0.60\ \mu$ curve only.

photons ρ_0 of radius b. The result for diffuse reflectance R is

$$R = \frac{2\omega}{d} \sum_{n=1}^{\infty} A_n[1 - (-1)^n e^{-d/\lambda}](Y - Z) \qquad (36)$$

where

$$Y = \lambda_n b[K_0(\lambda_n b)I_1(\lambda_n b) + I_0(\lambda_n b)K_1(\lambda_n b)]$$

$$Z = \frac{2a}{\lambda_n b^2} I_1(\lambda_n b)K_1(\lambda_n a)$$

$$A_n = \frac{\lambda}{1 + \left(\frac{\lambda}{\lambda_d}\right)^2 + \left(\frac{n\pi\lambda}{d}\right)^2 + \left(\frac{d}{n\pi\lambda_d}\right)^2}$$

and a is the radius of the receiving aperture.

We are now in a position to make quantitative comparison of the optical photon diffusion theory with experimental results on whole blood. Assuming absorption changes with wavelength proportional to the specific absorption coefficient κ, and scattering changes due to changing hematocrit by (28), a comparison of (36) with experimental results [105] is shown in Fig. 32. Peak reflectance is normalized to the experimental peak reflectance for the $\lambda = 0.60$ data only. The experimental data points compare encouragingly well with the diffusion theory. This approach is now being used to help understand a variety of optical propagation effects in biological materials and to help design optical bioinstrumentation.

F. Optical Bioinstrumentation

The absorbing of scattering properties of biological materials can be utilized to make important material property measurements. For example, knowing the specific absorption coefficient of a molecular species, the concentration can be obtained by an optical absorption measurement. In a clinical chemistry laboratory, various reagents are combined with specific biologically important ions and molecules to generate new colored compounds especially suited to optical measurements. A vast and automated technology has been built up based on this procedure.

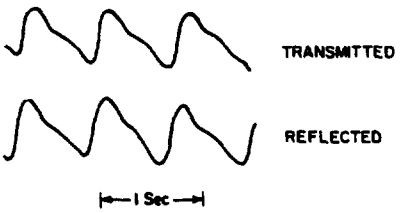

Fig. 33. Finger transmittance and reflectance pulsations at the heart rate.

Optics technology has also been applied to making important measurements on natural biological tissue. Two important applications will be discussed; the propagation of light through the skin and underlying tissue to measure blood volume (photoplethysmography) or anatomy (transilluminaltion), and optical spectrophotometric techniques to measure oxygen content in blood (oximetry).

1) Transillumination and Photoplethysmography: Cellular tissue is relatively transparent in the near infrared compared to the visible, transmitting from 2 to 3 percent in a 1-cm-thick sample [134]. However, blood is about 100 times more absorbing [135]. Obviously, air-filled structures, such as sinus cavities and the oral cavity, and clear fluid-filled structures, such as certain types of cysts and cerebrospinal fluid in the brain, absorb very little optical radiation. These gross discrepancies in optical absorption can be used to make qualitative judgments about the amount of a specific tissue type in an illuminated area. For example, by illuminating the oral cavity and sinuses, it can be determined by transmitted light through the face whether the sinuses are clear or congested. Transillumination of cysts in the testes has proved useful in determining whether the cysts are solid or accumulations of water.

Hydrocephalis (water on the brain) in infants is caused when the circulation of cerebrospinal fluid in the brain and spinal column is obstructed. When this occurs, the head is enlarged by pockets of clear fluid. The location and extent of this fluid can be observed by the use of a flashlight or chielded lamp in a darkened room [136]. A pulsed infrared transillumination device has been developed which can quantitatively measure head optical density [137].

The very large difference in absorption between blood and tissue in the near infrared means that transilluminated tissue total absorption may show periodic changes due to changes in tissue blood volume. This effect has been used to obtain indications of peripheral blood volume and pulse volume changes. This technique is termed photoplethysmography [138] and has been used to look at changes in the distribution of blood flow due to a variety of physiological causes. Reflected and transmitted light patterns give very similar results, as expected from the diffusion-like optical propagation processes involved [139]. Typical transmittance and reflectance variations with time through a finger are shown in Fig. 33.

2) Oximetry: One of the principal applications of optical propagation in blood is for the determination of blood oxygen saturation *OS*. Spectrophotometric techniques for measuring *OS* using transmitted light have been developed. The blood is hemolyzed, releasing HbO_2 of concentration C_0 and Hb of concentrtaion C_r into solution.

It is convenient to introduce a new definition for κ in terms of OS.

$$\kappa = \kappa_r + OS(\kappa_0 - \kappa_r) \tag{37}$$

where κ_0 is the specific absorption coefficient for HbO_2 and κ_r is the specific absorption coefficient for Hb. From the data shown in Fig. 24, $\kappa_0 = 0.10 \times 10^6$ and $\kappa_r = 0.80 \times 10^6$ at $\lambda = 0.66$ μ, and $\kappa_0 = \kappa_r = 0.20 \times 10^6$ at $\lambda = 0.80$ μ. This expression states that the average κ of the two-species medium consists of a simple average of the two coefficients in proportion to their relative concentrations. With this expression introduced into (12), one obtains

$$OD = 0.4343Cd[\kappa_r + OS(\kappa_0 - \kappa_r)]$$

where $C = C_0 + C_r$ is the total hemoglobin concentration. Measurements at two wavelengths are made, commonly near 0.66 μ where a large difference exists between the specific absorption coefficients for the two species of hemoglobin, and at 0.80 μ where the two specific absorption coefficients are equal. The ratio of the two optical densities yields a result for OS:

$$OS = \frac{\kappa_{r1}}{\kappa_{r1} - \kappa_{01}} - \frac{\kappa_{r2}}{\kappa_{r1} - \kappa_{01}} \frac{OD\text{ (red)}}{OD\text{ (infrared)}} \tag{38}$$

where subscript 1 refers to the red wavelength and subscript 2 refers to $\lambda = 0.80$ μ. In practice, one uses $OS = A - B\ OD(\text{red})/OD(\text{infrared})$, where A and B are constants obtained from a calibration procedure. An oximeter instrument measures the two OD values, performs the indicated algebraic operations in (38), and presents the OS value. A popular instrument of this type is the Instrumentation Laboratories model 182 CO-oximeter [140].

Oxygen saturation determinations can also be made using light reflected from whole blood. Reflection oximetry is convenient because it is unnecessary to hemolyze the blood and pass it through special apparatus. One commercially available instrument requires the deposition of a small amount of whole blood into a glass cylinder [141]. Light is reflected from the base of the cylinder and monitored to make the determination of OS. Another technique for measuring OS continuously in the living body involves the use of a fiberoptic catheter [142]–[148] in which fiberoptics are used to carry light to and from a measuring site. The reflectance equation for a semi-infinite medium, given in (19), provides the basis for this instrument. In order to determine OS, it is convenient to define σ_a in a way analogous to (37):

$$\sigma_a = \sigma_{ar} + OS(\sigma_{a0} - \sigma_{ar}) \tag{39}$$

where σ_{ar} is the average absorption cross section of an erythrocyte containing only Hb, and σ_{a0} is the average absorption cross section of an erythrocyte containing only HbO_2. The backscattering cross section σ_s^- is assumed not to vary with OS or wavelength over a limited range. The ratio of backscattered light intensity at infrared and red wavelengths has been shown from empirical studies to be related to OS by

$$OS = A - B\frac{R\text{ (infrared)}}{R\text{ (red)}} \tag{40}$$

where A and B are constants that depend on blood parameters. This result can be approximately obtained from (19). Moaveni [149] has determined approximate values for average erythrocyte cross sections at $\lambda = 0.80$ μ and $H = 0.42$ of $\sigma_s^- = 0.47$ μ^2 and $\sigma_a = 0.12$ μ^2. Using these cross-sectional values and inferring changes in σ_a with wavelength proportional to the specific absorption coefficient for hemoglobin, as shown in Fig. 24, (19) and (39) can be used to plot theoretical OS versus infrared to red reflectance ratio curves. For $\lambda_r = 0.66$ μ, and infrared wavelengths of 0.80, 0.92, and 1.00 μ, theoretical results in Fig. 34 show nearly linear curves for $\lambda_{ir} = 0.80$ μ and 0.92 μ, agreeing with the empirical result of (40).

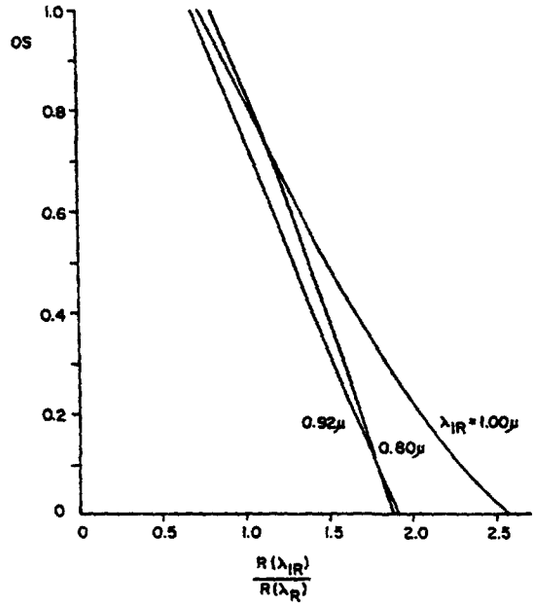

Fig. 34. Theoretical plot of oxygen saturation versus infrared-to-red reflectance ratio for three different infrared wavelengths. Red wavelength is $\lambda = 0.66$ μ.

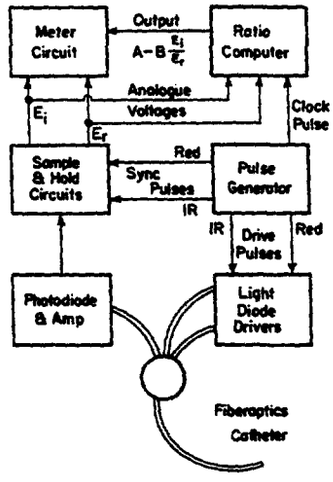

Fig. 35. Block diagram of fiberoptic catheter oximeter using pulsed light-emitting diodes.

Fortunately, gallium arsenide phosphide and gallium arsenide light-emitting diodes are available at $\lambda \cong 0.65$ μ and $\lambda \cong 0.92$ μ so that practical instruments can be developed with linear output [148]. Such an instrument is illustrated in Fig. 35 in block-diagram form. Three sets of intermeshed fiberoptic strands are located in a hollow tube called a catheter. Two sets of fiberoptic strands transmit red and infrared light to the tip of the catheter, while a third set of fibers transmit light reflected from blood at the tip of the catheter back to a

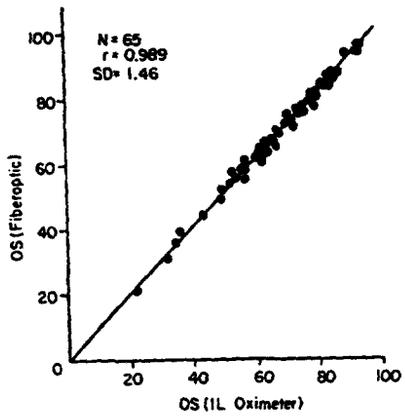

Fig. 36. Calibration plot showing correlation between oxygen saturation determined by the fiberoptic catheter oximeter and simultaneously drawn samples analyzed by the CO-oximeter. *In vivo* results were obtained from the adult catheterization laboratory and the coronary care unit.

photodetector. A pulse generator develops a 200-Hz square-wave pulse train which triggers the driving circuits for the light-emitting diodes. The diodes are pulsed alternately, producing two separate channels of red and infrared wavelengths, respectively. The spectral width of the light-emitting diodes is approximately 40 nm. The pulse generator also sends synchronous pulses to sample-and-hold circuits so that when the red light-emitting diode is turned on, a channel to the red circuit is opened; when the infrared light-emitting diode is turned on, a channel to the infrared circuit is open. Reflected red and infrared light returning from the blood is detected, amplified, and sent to sample-and-hold circuits. The output of the sample-and-hold circuits are two analog voltages E_r and E_i corresponding to the levels of red and infrared reflectance, respectively. The ratio of these two reflectance levels is proportional to the *OS* as given in (40). A direct conversion to *OS* can be made by introducing the A and B constants determined from calibration experiments. *In vivo* results, given in Fig. 36, show good correlation between *OS* determined by the Instrumentation Laboratories CO-oximeter and the fiberoptic catheter oximeter.

Acknowledgment

The information compiled in this paper is due to the contributions of many people. The authors specifically wish to thank the following for their assistance: Dr. J. Lehmann; Dr. H. Ho; C. Sorenson; J. McDougall; Dr. F. Harris; Dr. C. H. Durney; P. Cheung; J. Cole, M.D.; P. Hayden, M.D.; L. Reynolds; Dr. M. Moaveni; Dr. J. Shaken; and Dr. A. Ishimaru.

References

[1] F. B. Moor, "Microwave diathermy," in *Therapeutic Heat and Cold*, S. Licht, Ed. New Haven, Conn.: Licht, 1965, sec. 12, pp. 310–320.

[2] H. P. Schwan, "Biophysics of diathermy," in *Therapeutic Heat and Cold*, S. Licht, Ed. New Haven, Conn.: Licht, 1965, sec. 3, pp. 63–125.

[3] C. J. Restall, P. F. Leonard, H. F. Taswell, and R. E. Holaday. "Warming of human blood by use of microwaves," in *Summ. 4th IMPI Symp.* (Univ. of Alberta, Edmonton, Canada, May 21–23, 1969), pp. 96–99.

[4] R. P. Zimmer, H. A. Ecker, and V. P. Popovic, "Selective electromagnetic heating of tumors in animals in deep hypothermia," *IEEE Trans. Microwave Theory Tech.* (*Special Issue on Biological Effects of Microwaves*), vol. MTT-19, pp. 238–245, Feb. 1971.

[5] *An Act.* Public Law 90–602, 90th Cong., H. R. 10790, Oct. 18, 1968.

[6] W. Moore, Jr., *Biological Aspects of Microwave Radiation—A Review of Hazards.* U. S. Dep. HEW, PHS, Rep. TSB-68-4.

[7] M. Rosenstein, W. A. Brill, and C. K. Showalter, *Radiation Exposure Overview—Microwave Ovens and the Public.* U. S. Dep. HEW, PHS. Rep. OCS 69-1, July 1969.

[8] S. M. Michaelson, R. A. E. Thomson, and J. W. Howland, *Biologic Effects of Microwave Exposure.* Radiation Control for Health and Safety Act of 1967, Hearings before the Committee on Commerce, U. S. Senate, 90th Cong., 2nd Session, S.2067, S.3211, and H.F.10790, pp. 1443–1551.

[9] S. M. Michaelson, "The tri-service program—A tribute to George M. Knauf, USAF (MC)," *IEEE Trans. Microwave Theory Tech.* (*Special Issue on Biological Effects of Microwaves*), vol. MTT-19, pp. 131–146, Feb. 1971.

[10] ——, "Human exposure to nonionizing radiant energy—Potential hazards and safety standards," *Proc. IEEE*, vol. 60, pp. 389–421, Apr. 1972.

[11] C. J. Imig, J. D. Thomson, and H. M. Hines. "Testicular degeneration as a result of microwave irradiation," *Proc. Soc. Exper. Biol. and Med.*, vol. 69, pp. 382–386, Nov. 1948.

[12] B. O. Scott, "Short wave diathermy," in *Therapeutic Heat and Cold*, S. Licht, Ed. Baltimore, Md.: Waverly, 1958, pp. 255–283.

[13] F. H. Krusen, J. F. Herrick, U. Leden, and K. G. Wakim, "Microkymatotherapy; Preliminary report of experimental studies of heating effects of microwaves (radar) in living tissues," in *Proc. Staff Meet. Mayo Clin.*, vol. 22, p. 209, 1947.

[14] J. F. Lehmann, "Diathermy," in *Handbook of Physical Medicine and Rehabilitation*, Krusen, Kottke, Ellwood, Eds. Philadelphia, Pa.: Saunders, 1976.

[15] J. F. Herrick, "Peral-chain formation," in *Proc. 2nd Tri-Service Conf. Biol. Effects Microwave Energy*, University of Va., Charlottesville, Tech. Rep. ARDC-1 TR-58-54, ASTIA Doc. 131 477, pp. 83–93, 1958.

[16] J. Heller, "Effect of high-frequency electromagnetic fields on microorganisms," *Radio Electron.*, vol. 6, 1959.

[17] J. Heller, and A. A. Teixeira-Pinto, "A new physical method of creating chromosomal aberration," *Nature*, vol. 183, p. 905, 1959.

[18] J. Heller, and G. Mickey. "Non-thermal effects of radio frequency in biological systems," in *Dig. Int. Conf. Electronics*, vol. 21, p. 2, 1961.

[19] A. Wildervank *et al.*, "Certain experimental observations on a pulsed diathermy machine," *Arch. Phys. Med.*, vol. 40, p. 45, 1959.

[20] M. Satio *et al.*, "R- F- field-induced forces on microscopic particles," in *Dig. Int. Conf. Med. Electronics*, vol. 21, p. 3, 1961.

[21] M. Satio *et al.*, "The time constants of pearl chaim formation," in *Biological Effects of Microwave Radiation*, vol. 1. New York: Plenum, 1961, p. 85.

[22] A. Furedi and R. Valentine, "Factors involved in the orientation of microscopic particles in suspensions influenced by radio-frequency fields," *Biochim. Biophys. Acta*, vol. 56, p. 33, 1962.

[23] A. Furedi and I. Ohad, "Effects of high-frequency electric fields on the living cell," *Biochim. Biophys. Acta*, vol. 79, p. 1, 1964.

[24] A. S. Presman, *Electromagnetic Fields and Life.* New York: Plenum, 1970, pp. 59–61.

[25] H. Schwan, "Molecular response characteristics to ultra-high frequency fields," in *Proc. 2nd Tri-Serv. Conf. on Biol. Effects of Microwave Energy* (Rome, N. Y.), p. 33, 1958.

[26] J. Fleming *et al.*, "Microwave radiation in relation to biological systems and neural activity," in *Biological Effects of Microwave Radiation.* New York: Plenum, 1961, p. 239.

[27] D. A. Frank-Kamenetskii, "Plasma effects in semiconductors and biological effect of radiowaves," *Dokl. Akad. Nauk.* (USSR), vol. 136, pp. 476–478, 1961.

[28] A. S. Presman, "The physical basis for the biological action of centimeter waves," *Achiev. Mod. Biol.* (USSR), vol. 11, pp. 40–54, Libr. Cong., Washington, D. C., ATD P 65-17, 1956.

[29] J. E. Roberts, and H. F. Cook. "Microwaves in medical and biological research," *Brit. J. Appl. Physiol.*, vol. 3, pp. 33–39, 1952.

[30] A. S. Presman, I. Yu. Kamensky, and A. N. A. Levitina. "The biological effect of microwaves," *Achiev. Mod. Biol.* (USSR), vol. 51, pp. 84–103, Libr. Cong., Washington, D. C., ATD P 65–68, 1961.

[31] A. A. Teixeira-Pinto, L. L. Nejelski, J. L. Cutter, and J. H. Heller, "The behavior of unicellular organisms in an electromagnetic field," *Exp. Cell. Res.*, vol. 20, pp. 548–564, 1960.

[32] F. A. Brown, Jr., "Response to pervasive geophysical factors and the biological clock problem," *Symp. Quant. Biol.*, vol. 25, pp. 57–70, 1960.

[33] ——, "Extrinsic rhythmicality: A reference frame for biological rhythms under so-called constant conditions," in *Rhythmic Functions in the Living System.* New York: New York Acad. Sci., 1961; also in *Ann. N. Y. Acad. Sci.*, vol. 98, pp. 775–778.

[34] J. A. Tanner, "Effect of microwaves on birds," *Nature*, vol. 210, p. 636, 1966.

[35] A. H. Frey, "Auditory system response to RF energy," *Aerospace Med.*, vol. 32, pp. 1140–1142, 1961.

[36] ——, "Human auditory system response to modulated electromag

netic energy," *J. Appl. Physiol.*, vol. 17, pp. 689–692, 1962.
[37] H. C. Sommer, and H. E. von Gierke, "Hearing sensations in electric fields," *Aerospace Med.*, vol. 35, p. 834, 1964.
[38] Yu. A. Kholodov, "The effect of an electromagnetic field on the central nervous system," *Priroda* (USSR), vol. 4, pp. 104–105, Libr. Cong., Washington, D. C., ATD P 65–68, FTD-TT 62-1107., ASTIA Doc. 284 123, 1962.
[39] ——, "Effect of a UHF electromagnetic field on the electrical activity of a neuronally isolated region of the cerebral cortex," *Bull. Exp. Biol. Med.* (USSR), vol. 57, pp. 98–104, Libr. Cong., Washington, D. C., ATF P 65–68, 1964.
[40] ——, "The effect of electromagnetic and magnetic fields on the central nervous system," NASA Technical Translation, TTF-465, Washington, D. C. 1967.
[41] A. H. Frey, "Brain stem evoked responses associated with low intensity pulsed UHF energy," *J. Appl. Physiol.*, vol. 23, pp. 984–988, Dec. 1967.
[42] ——, "Biological function as influenced by low-power modulated RF energy," *IEEE Trans. Microwave Theory Tech.* (*Special Issue on Biological Effects of Microwaves*), vol. MTT-19, pp. 153–164, Feb. 1971.
[43] S. F. Korbel, "Behavioral effects of low intensity UHF radiation," in *Biological Effects and Health Implications of Microwave Radiation* (Symp. Proc. Med. College of Virginia, Richmond, Va., Rep. RRH/DBE 70–2), pp. 180–184, Sept. 1969.
[44] S. F. Korbel and W. D. Thompson, "Behavior effects of stimulation by UHF radio fields," *Psychological Reps.*, vol. 17, pp. 595–602, 1965.
[45] H. P. Schwan and G. M. Piersol, "The absorption of electromagnetic energy in body tissues, pt. I," *Amer. J. Phys. Med.*, vol. 33, 371–404, , 1954.
[46] ——, "The absorption of electromagnetic energy in body tissues, pt. II," *Amer. J. Phys. Med.*, vol. 34, pp. 425–448, 1955.
[47] H. P. Schwan, "Electrical properties of tissues and cells," *Advan. Biol. Med. Phys.*, vol. 5, pp. 147–209, 1957.
[48] H. Cook, "The dielectric behavior of some types of human tissues at microwave frequencies," *Brit. J. Appl. Phys.*, vol. 2, p. 295, 1951.
[49] ——, "Dielectric behavior of human blood at microwave frequencies," *Nature*, vol. 168, p. 247, 1951.
[50] ——, "A comparison of the dielectric behavior of pure water and human blood at microwave frequencies," *Brit. J. Appl. Phys.*, vol. 3, p. 249, 1952.
[51] K. Cole and R. Cole, "Dispersion and absorption in dielectrics," *J. Chem. Phys.*, vol. 9, p. 34, 1941.
[52] H. Schwan, "Alternating current spectroscopy of biological substances," *Proc. IRE*, vol. 47, p. 1841–1855, Nov. 1959.
[53] A. W. Guy, and J. F. Lehmann, "On the determination of an optimum microwave diathermy frequency for a direct contact applicator," *IEEE Trans. Biomed. Eng.*, vol. BME-13, pp. 76–87, Apr. 1966.
[54] A. W. Guy, "Electromagnetic fields and relative heating patterns due to a rectangular aperture source in direct contact with bilayered biological tissue," *IEEE Trans. Microwave Theory Tech.* (*Special Issue on Biological Effects of Microwaves*), vol. MTT-19, pp. 214–223, Feb. 1971.
[55] J. A. Stratton, *Electromagnetic Theory*. New York: McGraw-Hill, 1941.
[56] A. Anne, "Scattering and absorption of microwaves by dissipative dielectric objects: The biological significance and hazard to mankind," Ph.D. dissertation, Univ. of Pennsylvania, Philadelphia, Pa., 106 p., Cont. NONR 551505, ASTIA Doc. 408 997, 1963.
[57] A. Anne, M. Satio, O. M. Salati, and H. P. Schwan, "Penetration and thermal dissipation of microwaves in tissues," Univ. of Pennsylvania, Philadelphia, Pa., Tech. Rep. RADC-TDR-62-244. Cont. AF 3-(602)-2344, ASTIA Doc. 284 981, 1962.
[58] ——, "Relative microwave absorption cross sections of biological significance," in *Biological Effects of Microwave Radiation*, vol. 1. New York: Plenum, 1960, pp. 153–176.
[59] A. R. Shapiro, R. F. Lutomirski, and H. T. Yura, "Induced fields and heating within a cranial structure irradiated by an electromagnetic plane wave," *IEEE Trans. Microwave Theory Tech.* (*Special Issue on Biological Effects of Microwaves*), vol. MTT-19, pp. 187–196, Feb. 1971.
[60] H. P. Schwan, "Survey of microwave absorption characteristics of body tissues," in *Proc. 2nd Tri-Serv. Conf. on Biol. Effects of Microwave Energy*, pp. 126–145, 1958.
[61] H. S. Ho, A. W. Guy, R. A. Sigelmann, and J. F. Lehmann, "Electromagnetic heating patterns in circular cylindrical models of human tissue," in *Proc. 8th Int. Conf. on Med. and Biol. Eng.* (Chicago, Ill., Sess. 27.4,), 1969.
[62] H. S. Ho, R. A. Sigelmann, A. W. Guy, and J. F. Lehmann, "Electromagnetic heating of simulated human limbs by aperture sources," in *Proc. 23rd Ann. Conf. on Eng. in Med. and Biol.* (Washington, D. C., 1970), p. 159.
[63] H. S. Ho, A. W. Guy, R. A. Sigelmann, and J. F. Lehmann, "Microwave heating of simulated human limbs by aperture sources," *IEEE Trans. Microwave Theory Tech.*, vol. MTT-19, pp. 224–231, Feb. 1971
[64] J. F. Lehmann, A. W. Guy, V. C. Johnston, G. D. Brunner, and J. W. Bell, "Comparison of relative heating patterns produced in tissues by exposure to microwave energy at frequencies of 2450 and 900 megacycles," *Arch. Phys. Med. Rehab.*, vol. 43, pp. 69–76, Feb. 1962.
[65] A. W. Guy, J. F. Lehmann, J. A. McDougall, and C. C. Sorensen, "Studies on therapeutic heating by electromagnetic energy," in *Thermal Problems in Biotechnology*. New York: ASME, 1968, pp. 26–45.
[66] P. F. Wacker and R. R. Bowman, "Quantifying hazardous electromagnetic fields: Scientific basis and practical considerations," *IEEE Trans. Microwave Theory Tech.* (*Special Issue on Biological Effects of Microwaves*), vol. MTT-19, pp. 178–187, Feb. 1971.
[67] H. P. Schwan, "Interaction of microwave and radio frequency radiation with biological systems," *IEEE Trans. Microwave Theory Tech.* (*Special Issue on Biological Effects of Microwaves*), vol. MTT-19, pp. 146–152, Feb. 1971.
[68] E. E. Aslan, "Electromagnetic radiation survey meter," *IEEE Trans. Instrum. Meas.*, vol. IM-19, pp. 368–372, Nov. 1970.
[69] A. W. Rudge, "An electromagnetic radiation probe for near-field measurements at microwave frequencies," *J. Microwave Power*, vol. 5, pp. 155–174, Nov. 1970.
[70] S. L. Osborne and J. N. Frederick, "Microwave radiations. Heating of human and animal tissues by means of high frequency current with wavelength of twelve centimeters (the microtherm)," *J. Am. Med. Assoc.*, vol 137, pp. 1036–1040.
[71] A. W. Richardson, T. D. Duane, and H. M. Hines, "Experimental lenticular opacities produced by microwave irradiations," *Arch. Phys. Med.*, vol. 29, pp. 765–769, Dec. 1948.
[72] J. F. Lehmann, G. D. Brunner, J. McMillan, D. R. Silverman, and V. C. Johnston, "Modification of heating patterns produced by microwaves at the frequencies of 2456 and 900 Mc. by physiologic factors in the human," *Arch. Phys. Med.*, vol. 45, pp. 555–563, Nov. 1964.
[73] J. F. Lehmann, V. C. Johnston, J. McMillan, D. R. Silverman, G. D. Brunner, and L. A. Rathbun, "Comparison of deep heating by microwaves at frequencies 2456 and 900 megacycles," *Arch. Phys. Med.*, vol. 46, pp. 307–314, Apr. 1965.
[74] J. F. Lehmann, D. R. Silverman, B. A. Baum, N. L. Kirk, and V. C. Johnston, "Temperature distributions in the human thigh, produced by infra-red, hot pack and microwave applications," *Arch. Phys. Med.*, vol. 47, pp. 291–299, May 1966. Abstract, in *Modern Med.*, Nov. 21, 1966.
[75] Private correspondence.
[76] A. W. Guy, F. A. Harris, and H. S. Ho, "Quantitation of the effects of microwave radiation on central nervous system function," in *Proc. 6th Ann. Int. Microwave Power Symp.* (Monterey, Calif., May 1971).
[77] A. W. Guy, "Analyses of electromagnetic fields induced in biological tissues by thermographic studies on equivalent phantom models," *IEEE Trans. Microwave Theory Tech.* (*Special Issue on Biological Effects of Microwaves*), vol. MTT-19, pp. 205–214, Feb. 1971.
[78] *Therapeutic Heat and Cold*. S. Licht, Ed. Baltimore, Md.: Waverly, 1958.
[79] A. A. Beisang, C. H. Mayo, N. Pace, R. C. Lillehei, and E. H. Graham, "Rapid thawing of extended semen with microwaves," in *Summ. 4th IMPI Symp.* (Univ. of Alberta, Edmonton, Canada, May 21–23), p. 89, 1969.
[80] A. A. Beisang, R. H. Deitzman, G. J. Motsay, E. H. Graham, and R. C. Lillehei, "Microwave absorption in frozen physiological solutions containing glycerine," in *Summ. 4th IMPI Symp.* (Univ. of Alberta, Edmonton, Canada, May 21–23), p. 94, 1969.
[81] Y. E. Moskalenko, "Utilization of superhigh frequencies in biological investigations," *Biophysics* (USSR) (English transl.), vol. 3, pp. 619–626, 1958.
[82] ——, "On the application of centimeter radio waves for electrodeless recordings of volume changes of biological objects," *Biophysics* (USSR) (English transl.), vol. 5, pp. 225–228, 1960.
[83] K. E. Lonngren, "An application of microwaves to medical research," in *Summ. 4th Ann. IMPI Symp.* (Univ. of Alberta, Edmonton, Canada, May 21–23), p. 91, 1969.
[84] H. P. Schwan, and P. O. Vogelhut, "Scientific uses: Microwave studies of biological systems. Microwave properties of bound water and macromolecules," in *Microwave Power Engineering*, vol. 2. New York: Academic Press, 1968, pp. 235–244.
[85] K. F. Lindmann, "Über eine durch ein Isotopen System von Spiral-Formigen Resonatoren erzeugte Rotation–Polarisation der elektromagnetischen Wellen," *Ann. Physik.*, vol. 63, pp. 621–644, 1920.
[86] M. H. Winkler, "An experimental investigation of some models for optical activity," *J. Phys. Chem.*, vol. 60, pp. 1656–1659, 1956.
[87] A. J. H. Vendrik and J. J. Vos, "Comparison of the stimulation of the warmth sense organ by microwave and infrared," *J. Appl. Physiol.*, vol. 13, pp. 435–449, 1958.
[88] E. Hendler, R. Crosbie, and J. D. Hardy, "Measurement of heating

of the skin during exposure to infrared radiation," *J. Appl. Physiol.*, vol. 12, pp. 177–185, 1958.
[89] E. Hendler and J. D. Hardy, "Infrared and microwave effects on skin heating and temperature sensation," *IRE Trans. Med. Electron.*, vol. ME-7, pp. 143–152, July 1960.
[90] E. Hendler, J. D. Hardy, and D. Murgatroyd, "Skin heating and temperature sensation produced by infrared and microwave irradiation," in *Temperature: Its Measurement and Control in Science and Industry*, vol. 3. New York: Reinhold, 1963, pp. 211–230.
[91] P. J. Wyatt, "Differential light scattering: A physical method for identifying living bacterial cells," *Appl. Opt.*, vol. 7, pp. 1879–1896, Oct. 1968.
[92] ——, "Identification of bacteria by differential light scattering," *Nature*, vol. 221, p. 1257, 1969.
[93] P. T. Phillips, "Evolution of an instrument, the differential I," *Bioscience*, vol. 21, p. 865, May 1971.
[94] R. J. Fiel, E. H. Mark, and B. R. Munson, "Small angle light scattering of bioparticles," *Arch. Biophys. Biochem.*, vol. 141, pp. 547–551, 1970.
[95] V. Twersky, "Absorption and multiple scattering by biological suspensions," *J. Opt. Soc. Amer.*, vol. 60, pp. 1084–1093, Aug. 1970.
[96] F. Daniels, Jr., J. C. Van der Leun, and B. E. Johnson, "Sunburn," *Sci. Amer.*, pp. 38–46, July 1968.
[97] G. Moreno, M. Lutz, and M. Bessis, "Partial cell irradiation by ultraviolet and visible light: Conventional and laser sources," *Int. Rev. Exp. Path.*, vol. 7, pp. 99–137, 1969.
[98] R. A. MacRae, J. A. McClure, and P. Latimer, "Spectral transmission and scattering properties of red blood cells," *J. Opt. Soc. Amer.*, vol. 51, pp. 1356–1372, 1961.
[99] R. Barer, "Spectrophotometry of clarified cell suspension," *Science*, vol. 121, pp. 709–715, May 1955.
[100] B. L. Horecker, "Absorption spectra of hemoglobin and its derivatives in the visible and near infrared regions," *J. Biol. Chem.*, vol. 148, pp. 173–183, 1943.
[101] T. J. Livesey, and F. W. Billmeyer, Jr., *J. Colloid Interface Sci.*, vol. 30, p. 447, 1969.
[102] R. F. Fiel, and H. M. Scheintaur, "Small angle light scattering by erythrocytes," *J. Colloid Interface Sci.*, vol. 37, pp. 249–250, Sept. 1971.
[103] D. K. Kreid, M. R. Kannin, R. J. Goldstein, "Measurements of light scattering characteristics of red cells, red cell 'ghosts' and polystyrene spheres," in *Proc. 24th Ann. Conf. on Eng. in Med. and Biol.* (Las Vegas, Nev., Oct.–Nov. 1971), p. 143.
[104] C. C. Johnson, "Near infrared propagation in blood," *J. Assc. Adv. Med. Instr.*, vol. 4, pp. 22–27, Jan.–Feb. 1970.
[105] N. M. Anderson and P. Sekelj, "Reflection and transmission of light by thin films of non-hemolysed blood," *Phys. Med. Biol.*, vol. 12, pp. 185–192, 1967.
[106] F. Urbach, Ed., *The Biologic Effects of Ultra-Violet Radiation.* New York: Pergamon, 1969.
[107] J. D. Hardy, H. T. Hammel, and D. Murgatroyd, "Spectral transmittance and reflectance of excised human skin," *J. Appl. Physiol.*, vol. 9, pp. 257–264, Sept. 1956.
[108] J. A. Jacquez and H. F. Kuppenheim, "Spectral reflectance of human skin in the region 235–1000mμ," *J. Appl. Physiol.*, vol. 7, pp. 523–528, 1955.
[109] J. A. Jacquez, J. Huss, W. McKeehan, J. M. Dimitroff, and H. F. Kuppenheim, "Spectral reflectance of human skin in the region 0.7–2.6μ," *J. Appl. Physiol.*, vol. 8, pp. 297–299, 1955.
[110] A. Schuster, "Radiation through a foggy atmosphere," *Astrophys. J.*, vol. 21, pp. 1–22, Jan. 1905.
[111] L. Silberstein, "The transparency of turbid media," *Phil. Mag.*, vol. 4, p. 1291, 1927.
[112] J. W. Ryde, "The scattering of light by turbid media—Part I," *Proc. Roy. Soc. London, Ser. A.*, vol. 131, p. 451, 1931.
[113] J. W. Ryde, and B. S. Cooper, "The scattering of light by turbid media—Part II," *Proc. Roy. Soc. London, Ser. A*, vol. 131, p. 464, 1931.
[114] P. Kubelka and F. Munk, "Ein Beitrag zur Optik der Farbanstriche," *Z. Tech. Physik*, vol. 12, p. 593, 1931.
[115] P. Kubelka, "New contributions to the optics of intensely light-scattering materials—Part I," *J. Opt. Soc. Amer.*, vol. 38, pp. 448–457, May 1948.
[116] S. Q. Duntley, "The optical properties of diffusing materials," *J. Opt. Soc. Amer.*, vol. 32, p. 61, 1942.
[117] R. G. Giovanelli, "A note on the coefficient of reflection for internally incident diffuse light," *Optica Acta*, vol. 3, p. 127, 1956.
[118] W. L. Butler, "Absorption of light by turbid materials," *J. Opt. Soc. Amer.*, vol. 52, p. 292, 1962.
[119] J. K. Beasley, J. T. Atkins, and F. W. Billmeyer, "Scattering and absorption of light in turbid media," in *Proc. 2nd Interdisc. Conf. on Elect. Scattering.* R. S. Stein and R. L. Rowell, Eds. New York: Gordon and Breach, 1967.
[120] L. Amy, "Sur la couleur des corps par reflexion," *Rev. Optique*, vol. 16, p. 81, 1937.
[121] F. A. Rodrigo, "The determination of the oxygenation of blood in vitro by using reflected light," *Am. Heart J.*, vol. 45, pp. 809–822, 1953.
[122] R. L. Longini and R. Zdrojkowski, "A note on the theory of backscattering of light by living tissue," *IEEE Trans. Biomed. Eng.*, vol. BME-15, pp. 4–10, Jan. 1958.
[123] V. Twersky, "Interface effects in multiple scattering by large, low-refracting, absorbing particles," *J. Opt. Soc. Amer.*, vol. 60, pp. 908–914, July 1970.
[124] S. Chandrasekhar, *Radiative Transfer.* New York: Dover, 1963.
[125] V. Kourganoff, *Basic Methods in Transfer Problems.* New York: Dover, 1963.
[126] V. Twersky, "On scattering of waves by random distribution," in *Proc. Am. Math. Soc. Symp. on Stocastic Processes in Math. Phys. and Eng.*, vol. 16. New York: McGraw Hill, 1964, pp. 84–166.
[127] R. J. Zdrojkowski and R. L. Longini, "Optical transmission through whole blood illuminated with highly collimated light," *J. Opt. Soc. Amer.*, vol. 59, pp. 893–903, Aug. 1969.
[128] C. C. Johnson, "Opital diffusion in blood," *IEEE Trans. Biomed. Eng.*, vol. BME-17, pp. 129–133, Apr. 1970.
[129] R. J. Zdrojkowski and N. Pisharoty, "Optical transmission and reflection by blood," *IEEE Trans. Biomed. Eng.*, vol. BME-17, pp. 122–128, Apr. 1970.
[130] A. Cohen and R. L. Longini, "Theoretical determination of the blood's relative oxygen saturation in vivo," *Med. Biol. Eng.*, vol. 9, pp. 61–69, 1971.
[131] L. O. Reynolds, "Three dimensional reflection and transmission equations for optical diffusion in blood," M. S. thesis, Elec. Eng. Dep., Univ. of Washington, Seattle, 1970.
[132] P. I. Richards, "Multiple isotropic scattering," *Phys. Rev.*, vol. 100, pp. 517–522, Oct. 1955.
[133] C. H. Durney, private communication.
[134] C. M. Cartwright, "Spectrotransmission of the human body," in *Medical Physics*, N. O. Glasser, Ed. Chicago, Ill.: Yearbook Publishers, 1944.
[135] K. Kramer, J. O. Elan, G. A. Saxton, and W. N. Elan, "Influence of oxygen saturation, erythrocyte concentration and optical depth on the red and near-infrared regions," *Am. J. Physiol.*, vol. 165, pp. 229–246, 1951.
[136] D. B. Shurtleff, E. L. Foltz, and D. Fry, "Clinical use of transillumination," *Arch. Dis. Childh.*, vol. 41, pp. 183–187, Apr. 1966.
[137] C. C. Johnson, B. Henshaw, and D. Watkins, "A pulsed transilluminator," in *Proc. 8th ICMBE* (Chicago, Ill., July, 1969), pp. 13–19.
[138] J. Weinman, "Photoplethysmography," ch. 6 in *A Manual of Psychophysiological Methods.* Amsterdam, The Netherlands: North-Holland, 1967.
[139] G. Uretzky and Y. Palti, "A method for comparing transmitted and reflected light photoelectric plethysmography," *J. Appl. Physiol.*, vol. 31, pp. 132–135, July 1971.
[140] A. H. J. Maas, M. L. Hamelink, and R. J. M. De Leeuw, "An evaluation of the spectrophotometric determination of HbO_2, HbCO, and Hb in blood with the CO-oximeter IL-182," *Clin. Chem. Acta*, vol. 29, pp. 303–309, 1970.
[141] M. L. Polanyi and R. M. Hehir, "New reflection oximeter," *Rev. Sci. Instrum.*, vol. 31, pp. 401–403, Apr. 1960.
[142] M. L. Polanyi and R. M. Hehir, "In vivo oximeter with fast dynamic response," *Rev. Sci. Instrum.*, vol. 33, pp. 1050–1054, Oct. 1962.
[143] Y. Enson, W. A. Briscoe, N. L. Polanyi, and A. Cournand, "In vivo studies with an intra-vascular and intracardiac reflection oximeter," *J. Appl. Phys.*, vol. 17, pp. 552–558, May 1962.
[144] P. L. Frommer, J. Ross, Jr., D. T. Mason, J. H. Gault, and E. Brunwald, "Clinical applications of an improved, rapidly responding fiberoptic catheter," *Am. J. Card.*, vol. 15, pp. 672–678, May 1965.
[145] W. J. Gamble, P. G. Hugenholtz, R. G. Monroe, M. Polanyi, and A. S. Nadas, "The use of fiberoptics in clinical cardiac catheterization, 1. Intracardiac oximetry," *Circulation*, vol. 31, Mar. 1965.
[146] D. C. Harrison, N. S. Kapany, H. A. Miller, N. Silbertrust, W. L. Henry, and R. P. Drake, "Fiberoptics for continuous in vivo monitoring of oxygen saturation," *Am. Heart J.*, vol. 71, pp. 766–774, June 1966.
[147] G. A. Mook, P. Osypka, R. E. Sturm, and E. H. Wood, "Fiberoptic reflection photometry on blood," *Cardiovas. Res.*, vol. 24, pp. 199–209, Apr. 1968.
[148] C. C. Johnson, R. D. Palm, D. C. Stewart, and W. E. Martin, "A solid-state fiberoptics oximeter," *J. Assn. Adv. Med. Instr.*, vol. 5, pp. 77–83, Mar.–Apr. 1971.
[149] M. K. Moaveni, "A multiple scattering field theory applied to whole blood," Ph.D. dissertation, Elec. Eng. Dep., Univ. of Washington, Seattle, 1970.